Evidence for Photochemical Radical Formation by β-Carbolines

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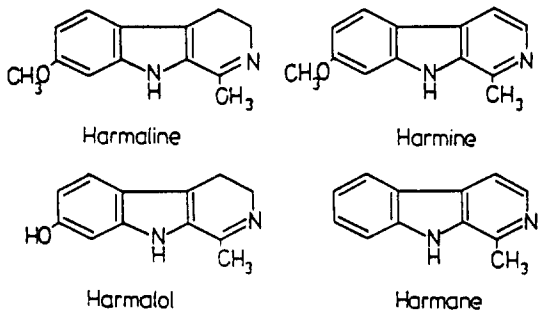
β-Carboline alkaloids are strongly fluorescent and pharmacologically interesting compounds because of the versatile biological activities such as antiviral and reversible inhibitors of monoamine oxidase. Recently, Mckenna *et. al.*[1] studied the UV mediated cytotoxic activity of β-carboline alkaloids using yeast and bacterial bioassay systems. The structure of β-carbolines is similar to certain tricyclic aromatic photosensitizers such as psoralen or acridine and they readily bind to native DNA.[2,3] It is very probable that the phototoxicity of β-carbolines may result from the photochemical alternation of DNA by the intercalated β-carbolines. However, nothing has been known about the mechanism of β-carboline induced photodamage.



Structure of β-carboline alkaloids.

Balsells *et. al.*[4] studied photodimerization of β-carbolines and isolated two photoproducts involving the formation of new N-N and N-C bonds. They suggested a radical mechanism for these dimerization reactions. In this paper, we report the photopolymerization of vinyl monomers initiated by β-carbolines as an evidence for the photochemical radical formation of these compounds. If radical species are formed on photolysis of the sensitizer, one should be able to initiate the photopolymerization of vinyl monomers by these compounds. The initiation of chain reactions by free radicals can serve as the direct evidence for the formation of these radicals. The polymerization of vinyl monomers has been used to detect free radicals in Fenton's reagent,[5,6] in illuminated solutions of chlorophyll[7] and in photosensitization by drugs.[8,9]

A typical reaction was carried out as follows: Irradiation of a 354 nm of UV light to a CCl_4-MeOH or THF-MeOH solution of β-carboline (5×10^{-4} M) and monomer (0.1 M) in anaerobic (N_2) condition led to polymerization of vinyl monomers. Vinyl monomers such as vinyl acetate (VA), acrylonitril (AN), styrene and methyl methacrylate (MMA) were efficiently polymerized. The polymerization proceeded only in the prescence of good radical transfering agents such as CCl_4 or THF. The polymerization did not take place in the absence of (1) light, (2) CCl_4 or THF, (3) β-carbolines. Thus, this polymerization cannot be explained by thermally induced polymerization.

Four carboline derivatives - harmane (1), harmine (2), harmalol (3) and harmaline (4) - were tested for their photopolymerization ability of vinyl monomers. Figure 1 shows the polymerization of acryl amide initiated by β-carbolines in CCl_4-MeOH (6:4, v/v). The polymerization ability increased in the order of (2) > (4) > (1) > (3). However, different result was obtained in THF: (1) and (2) showed high polymerization efficiency while (3) and (4) gave low efficiency. The relative photopolymerization rate of vinyl monomers increased in the order of VA > AN > styrene or MMA in CCl_4, and MMA > styrene > VA in THF. In addition, all these polymerizations were effectively inhibited by radical scavengers such as oxygen and benzoquinone indicating that these polymerizations proceed through a free radical mechanism and the radical which initiates the polymerization in CCl_4 is different from the radical produced in THF. The maximum polymerization rate was obtained at 60 % CCl_4 or THF in methanol as shown in Figure 2 suggesting the possibility of initiation of polymerization by the radicals derived from CCl_4 or THF.

The photopolymerization mechanism may different from solvent to solvent. The formation of charge transfer complex between amine and halocarbon has been reported.[10,11] The photoinitiation in CCl_4 solution can be envisioned as occuring through photodissociation of the CCl_4-carboline charge transfer complex into the chloride salt of carboline radical cation and trichloromethyl radical.[12,13] Then, the trichloromethyl radical possibly initiates the polymerization.

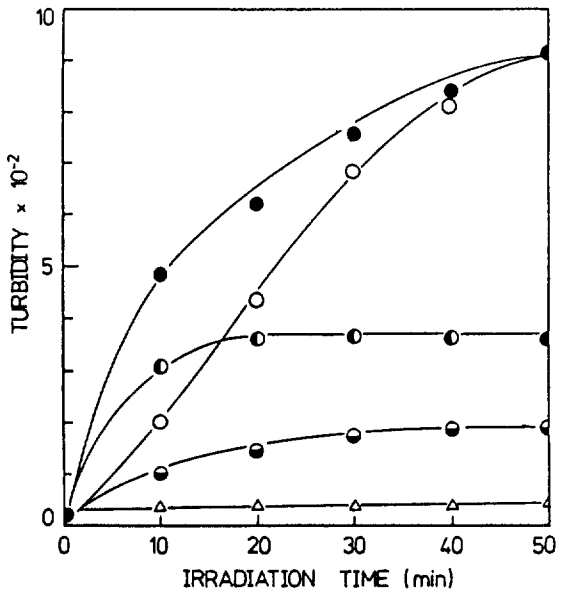


Figure 1. Turbidity change by photopolymerization of acryl amide initiated by β-carbolines (5×10^{-4}M) as a function of irradiation time in CCl_4-MeOH (6:4, v/v); harmine (-●-), harmaline (-○-), harmane (-◐-), harmalol (-◒-) and without sensitizer (-△-).

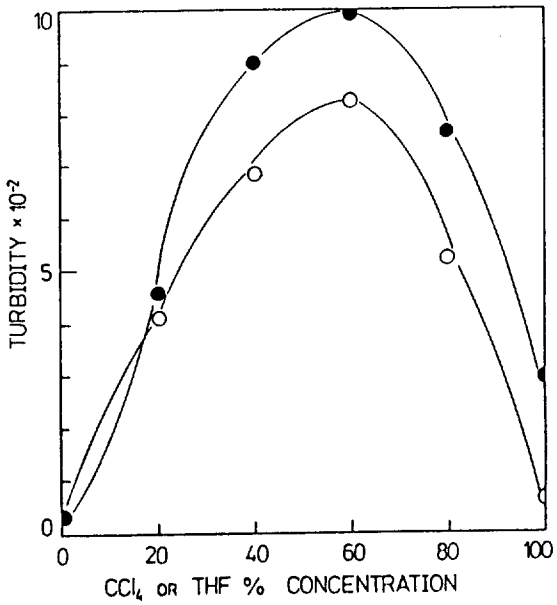


Figure 2. Turbidity change by photopolymerization of acryl amide (10^{-1} M) with harmaline (5×10^{-4} M) as a function of CCl_4 (-○-) or THF (-●-) % concentration in methanol.

The photopolymerization in THF solution may be explained as follows: The aminyl radicals are stable and can abstract hydrogen from solvents such as cyclohexane, THF and alkylbenzene.[14] The photoexcited β-carbolines fragment into 9-β-carbolinyl radical and hydrogen,[4] and the carbolinyl radical abstract hydrogen from THF. Then, the THF radical possibly initiates the polymerization.[15] The details of this reaction will be investigated in this laboratory.

Acknowledgment. This investigation was supported by the Korea Science and Engineering Foundation. The auther is grateful to Mr. June Shik Sung for his help and Prof. Sang Chul Shim of Korea Advanced Institute of Science and Technology for kind discussions.

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Conversion of Penicillin to Cephalosporin. Intramolecular Cyclization of a Penicillin-derived 4-mercaptoazetidin-2-one

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Since penicillin sulfoxides underwent an acidic rearrangement to cephalosporins,[1] many researchers have attempted to prepare cephalosporins from readily available penicillins. Azetidinones[2] and thiazolinoazetinones[3] are now well known as the intermediates in the preparation of cephalosporins.

Mercaptoazetinones have been proposed as intermediates on penicillin biosynthesis.[4] Free sulfhydryl compounds have not been directly used in the synthesis of β-lactam antibiotics. Disulfides, instead have often been employed as intermediates, which can be prepared from either penicillin sulfoxides[5] or thiazolinoazetidinones.[6]

Mercapto compounds can be prepared by simple hydrolysis of the corresponding thiazolinoazetidinones.[7,8] Using the sulfur compounds, intramolecular Michael reaction and other cyclizations were carried out in vain.[8]

We now wish to report utilization of mercapto compounds for the synthesis of β-lactam antibiotics. Thiazolinoazetidinone **1** was treated with 30% aq $HClO_4$ in the mixture of CH_2Cl_2 and acetone[8] to give mercaptan **2**.[9] By treatment with 2-mercaptobenzothiazole or 2-benzothiazolyl disulfide, the mercaptan could be converted to disulfide **3** which is one of the intermediates in the synthesis of β-lactam antibiotics.[5,6] The mercaptan was treated with 2-mercaptobenzothiazole in the presence of $NaIO_4$ to afford the disulfide in moderate yield. However, the disulfide can be given in higher yield by the known procedure.[5,6]

The mercaptan could not be converted to a β-lactam compound by treatment with m-chloroperoxybenzoic acid or chlorine[5] even in the presence of silver nitrate. The major product was dimer **4**. Photocyclization[10] of the mercaptan us-